DEPARTMENT OF HEALTH AND HUMAN SERVICES

DMB

Display Date 10-17-02

Publication Date 10-18-02

Certifier R LEDESMA

Food and Drug Administration

[Docket No. 02N–0296]

Agency Information Collection Activities; Submission for OMB Review; Comment Request; Investigational New Drug Regulations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that the proposed collection of information listed below has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Submit written comments on the collection of information by [*insert date 30 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit written comments on the collection of information to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Stuart Shapiro, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Karen L. Nelson, Office of Information Resources Management (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1482.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

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Investigational New Drug (IND) Regulations—Part 312 (21 CFR Part 312)—(OMB Control Number 0910–0014)—Extension

FDA is requesting OMB approval for the reporting and recordkeeping requirements contained in the FDA regulation "Investigational New Drug Application" part 312 (21 CFR part 312). This regulation implements provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)) to issue regulations under which the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products can be conducted.

FDA is charged with implementing statutory requirements that drug products marketed in the United States be shown to be safe and effective, properly manufactured, and properly labeled for their intended uses. Section 505(a) of the act provides that a new drug may not be introduced or delivered for introduction into interstate commerce in the United States unless FDA has previously approved a new drug application (NDA). FDA approves an NDA only if the sponsor of the application first demonstrates that the drug is safe and effective for the conditions prescribed, recommended, or suggested in the product's labeling. Proof must consist, in part, of adequate and well controlled studies, including studies in humans, that are conducted by qualified experts. The IND regulations establish reporting requirements that include an initial application as well as amendments to that application, reports on significant revisions of clinical investigation plans, and information on a drug's safety or effectiveness. In addition, the sponsor is required to give FDA an annual summary of the previous year's clinical experience. Submissions are reviewed by medical officers and other agency scientific reviewers assigned responsibility for overseeing the specific study. The IND regulations also

contain recordkeeping requirements that pertain to the responsibilities of sponsors and investigators. The detail and complexity of these requirements are dictated by the scientific procedures and human subject safeguards that must be followed in the clinical tests of investigational new drugs.

The IND information collection requirements provide the means by which FDA can: (1) Monitor the safety of ongoing clinical investigations; (2) determine whether the clinical testing of a drug should be authorized; (3) ensure production of reliable data on the metabolism and pharmacological action of the drug in humans; (4) obtain timely information on adverse reactions to the drug; (5) obtain information on side effects associated with increasing doses; (6) obtain information on the drug's effectiveness; (7) ensure the design of well-controlled, scientifically valid studies; (8) obtain other information pertinent to determining whether clinical testing should be continued and information related to the protection of human subjects. Without the information provided by industry in response to the IND regulations, FDA cannot authorize or monitor the clinical investigations which must be conducted before authorizing the sale and general use of new drugs. These reports enable FDA to monitor a study's progress, to assure subject safety, to assure that a study will be conducted ethically, and to increase the likelihood that the sponsor will conduct studies that will be useful in determining whether the drug should be marketed and available for use in medical practice.

There are two forms that are required under part 312:

Form FDA–1571—"Investigational New Drug Application." A person who intends to conduct a clinical investigation submits this form to FDA. It includes: (1) A cover sheet containing background information on the sponsor

and investigator; (2) a table of contents; (3) an introductory statement and general investigational plan; (4) an investigator's brochure describing the drug substance; (5) a protocol for each planned study; (6) chemistry, manufacturing, and control information for each investigation; (7) pharmacology and toxicology information for each investigation; and (8) previous human experience with the investigational drug.

Form FDA–1572—"Investigator Statement." Before permitting an investigator to begin participation in an investigation, the sponsor must obtain and record this form. It includes background information on the investigator and the investigation, and a general outline of the planned investigation and the study protocol.

FDA is requesting OMB approval for the following reporting and recordkeeping requirements in part 312:

TABLE 1.—REPORTING REQUIREMENTS

21 CFR Section	Explanations
312.7(d)	Applications for permission to sell an investigational new drug.
312.10(a)	Applications for waiver of requirements under part 312. Estimates for this requirement are included under §§312.23 and 312.31.
312.20(c)	Applications for investigations involving an exception from informed consent under §50.24 (21 CFR 50.24). Estimates for this requirement are included under §312.23.
312.23	INDs (content and format).
312.23(a)(1)	Cover sheet FDA–1571.
312.23(a)(2)	Table of contents.
312.23(a)(3)	Investigational plan for each planned study.
312.23(a)(5)	Investigator's brochure.
312.23(a)(6)	Protocols—Phase 1, 2, and 3.
312.23(a)(7)	Chemistry, manufacturing, and control information.
312.23(a)(7)(iv)(*a*),(*b*),(*c*)	A description of the drug substance, a list of all components, and any placebo used.
312.23(a)(7)(iv)(*d*)	Labeling: Copies of labels and labeling to be provided each investigator.
312.23(a)(7)(iv)(*e*)	Environmental impact analysis regarding drug manufacturing and use.
312.23(a)(8)	Pharmacological and toxicology information.
312.23(a)(9)	Previous human experience with the investigational drug.
312.23(a)(10)	Additional information.
312.23(a)(11)	Relevant information.
312.23(f)	Identification of exception from informed consent.
312.30	Protocol amendments.
312.30(a)	New protocol.
312.30(b)	Change in protocol.
312.30(c)	New investigator.
312.30(d)	Content and format.
312.30(e)	Frequency.
312.31	Information amendments.
312.31(b)	Content and format.
	Chemistry, toxicology, or technical information.
312.32	Safety reports.
312.32(c)(1)	Written reports to FDA and to investigators.
312 32(c)(2)	Telephone reports to FDA for fatal or life-threatening experience.
312.32(c)(3)	Format or frequency.
312.32(d)	Follow up submissions.
312.33	Annual reports.
312.33(a)	Individual study information.
312.33(b)	Summary information.
312.33(b)(1)	Adverse experiences.
312.33(b)(2)	Safety report summary.

TABLE 1.—REPORTING REQUIREMENTS—Continued

21 CFR Section	Explanations
312.33(b)(3)	List of fatalities and causes of death.
312.33(b)(4)	List of discontinuing subjects.
312.33(b)(5)	Drug action.
312.33(b)(6)	Preclinical studies and findings.
312.33(b)(7)	Significant changes.
312.33(c)	Next year general investigational plan.
312.33(d)	Brochure revision.
312.33(e)	Phase I protocol modifications.
312.33(f)	Foreign marketing developments.
312.35	Treatment use of investigational new drugs.
312.35(a)	Treatment protocol submitted by IND sponsor.
312.35(b)	Treatment IND submitted by licensed practitioner.
312.36	Requests for emergency use of an investigational new drug.
312.38(b) and (c)	Notification of withdrawal of an IND.
312.42(e)	Sponsor requests that a clinical hold be removed and submits a complete response to the issues identified in the clinical hold order.
312.44(c) and (d)	Opportunity for sponsor response to FDA when IND is terminated.
312.45(a) and (b)	Sponsor request for or response to inactive status determination of an IND.
312.47(b)	"End-of-Phase 2" meetings and "Pre-NDA" meetings.
312.53(c)	Investigator information.
	Investigator report (Form FDA–1572) and narrative; Investigator's background information; phase 1 outline of planned investigation; and phase 2 outline of study protocol; financial disclosure information.
312.54(a) and (b)	Sponsor submissions concerning investigations involving an exception from informed consent under § 50 24.
312.55(b)	Sponsor reports to investigators on new observations, especially adverse reactions and safe use. Only "new observations" are estimated under this section; investigator brochures are included under § 312.23.
312.56(b), (c), and (d)	Sponsor monitoring of all clinical investigations, investigators, and drug safety; notification to FDA.
312.58(a)	Sponsor's submission of records to FDA on request.
312.64	Investigator reports to the sponsor.
312.64(a)	Progress reports.
312.64(b)	Safety reports
312.64(c)	Final reports.
312.64(d)	Financial disclosure reports.
312.66	Investigator reports to Institutional Review Board. Estimates for this requirement are included under § 312.53.
312.70(a)	Investigator disqualification; opportunity to respond to FDA.
312.83	Sponsor submission of treatment protocol. Estimates for this requirement are included under §§ 312 34 and 312.35.
312.85	Sponsors conducting phase 4 studies. Estimates for this requirement are included under § 312.23, and under 21 CFR 314.50, 314.70, and 314.81 in 0910–0001.
312.110(b)	Request to export an investigational drug.
312.120(b) and (c)(2)	Sponsor's submission to FDA for use of foreign clinical study to support an IND.
312.120(c)(3)	Sponsor's report to FDA on findings of independent review committee on foreign clinical study.
312.130(d)	Request for disclosable information for investigations involving an exception from informed consent under § 50.24.

TABLE 2.—RECORDKEEPING REQUIREMENTS

21 CFR Section	Explanations
312.52(a)	Transfer of obligations to a contract research organization.
312.57(a) and (b)	Sponsor recordkeeping.
312.59	Sponsor recordkeeping of disposition of unused supply of drugs. Estimates for this requirement are included under § 312.57.
312.62(a)	Investigator recordkeeping of disposition of drugs.
312.62(b)	Investigator recordkeeping of case histories of individuals.
312.160(a)(3)	Records maintenance: Shipment of drugs for investigational use in laboratory research animals or in vitro tests.
312.160(c)	Shipper records of alternative disposition of unused drugs.

In tables 3 through 5 of this document, the estimates for "number of respondents," "number of responses per respondent," and "total annual responses" were obtained from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) reports and data management systems for submissions received in 2001 and from other

sources familiar with the number of submissions received under part 312. The estimates for "hours per response" were made by CDER and CBER individuals familiar with the burden associated with these reports and from estimates received from the pharmaceutical industry. Although the number of submissions may fluctuate, e.g., due to the addition of respondents not previously required to comply with part 312 or due to the normal variation in annual submissions, this variable is not reflected in the burden totals because the overall rate of submissions are not expected to change significantly over the next few years. In the **Federal Register** of July 22, 2002 (67 FR 47811), the agency requested comments on the proposed collection of information. No comments were received on that request.

TABLE 3.—ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN FOR HUMAN DRUGS[1]

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
312.7(d)	5	1.4	7	24	168
312.23(a) through (f)	1,506	1.2	1,872	1,600	2,995,200
312.30(a) through (e)	1,050	15	15,705	284	4,460,220
312.31(b)	1,037	8	8,375	100	837,500
312.32(c) and (d)	546	22.6	12,366	32	395,712
312.33(a) through (f)	1,608	2.6	4,202	360	1,512,720
312.35(a) and (b)	1	1	1	300	300
312.36	281	1	302	16	4,832
312.38(b) and (c)	466	1.3	608	28	17,024
312.42(e)	63	1.2	78	284	22,152
312.44(c) and (d)	40	1	42	16	672
312.45(a) and (b)	244	1.4	355	12	4,260
312.47(b)	130	1.8	233	160	37,280
312.53(c)	20,428	1	20,428	80	1,634,240
312.54(a) and (b)	1	1	1	48	48
312.55(b)	388	435	168,775	48	8,101,200
312.56(b), (c), and (d)	2	1	2	80	160
312.58(a)	75	4.2	322	8	2,576
312.64(a) through (d)	11,574	3	34,722	24	833,328
312.70(a)	2	1	2	40	80
312.110(b)	32	8.1	261	75	19,575
312.120(b) and (c)(2)	180	2	361	168	60,548
312.120(c)(3)	2	2	4	40	160
312.130(d)	4	1	4	8	32
312.52(a)	1,104	3 .1	3,495	2	6,990
312.57(a) and (b)	1,104	34.5	38,088	100	3,808,800
312.62(a)	9,522	2	19,044	40	761,760
312.62(b)	9,522	10	95,220	40	3,808,800
312.160(a)(3)	301	1.4	425	.5	213
312.160(c)		1.4	425	.5.	213
Total					29,326,763

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 4.—ESTIMATED ANNUAL REPORTING BURDEN FOR BIOLOGICS[1]

21 CFR Section	No. of Respondents	No. of Responses per Response	Total Annual Responses	Hours per Responses	Total Hours
312.7(d)	22	1.4	31	24	744
312.10(a)	9	7 9	71	40	2,840
312.23(a) and (f) and 312.120(b), (c)(2), and (c)(3)	376	1.4	535	1,600	856,000
312.30(a) through (e)	724	5.6	4,038	284	1,146,792
312.31(b)	268	9.0	2,399	100	239,900

TABLE 4.—ESTIMATED ANNUAL REPORTING BURDEN FOR BIOLOGICS[1]—Continued

21 CFR Section	No. of Respondents	No. of Responses per Response	Total Annual Responses	Hours per Responses	Total Hours
312.32(c) and (d) and 312.56(c)	334	12.8	4,261	32	136,352
312.33(a) and (f) and 312.56(c)	614	2.6	1,615	350	565,250
312.35(a) and (b)	1	1	1	300	300
312.36	19	4	76	16	1,216
312.38(b)	172	2.1	358	28	10,024
312.38(c)	172	2.1	358	160	57,280
312.44(c) and (d)	0	0	0	0	0
312.45(a) and (b)	70	1.7	120	12	1,440
312.47(b)	60	1.1	68	160	10,880
312.53(c)	322	5.9	1,904	80	152,320
312.54(a) and (b)	0	0	0	0	0
312.55(b)	139	2.4	331	48	15,888
312.56(b) and (d)	12	1.7	20	80	1,600
312.58(a)	19	1	19	8	152
312.64(a) and (d)	5,713	1	5,713	24	137,112
312.110(b)	9	2.4	22	75	1,650
312.130(d)	1	1	1	0.5	0.5
Total					3,337,740.5

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 5.—ESTIMATED ANNUAL RECORDKEEPING BURDEN FOR BIOLOGICS[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
312.52(a) recordkeeping	113	1	113	5	565
312.57(a) and (b) recordkeeping	1,432	2	2,859	100	285,900
312.62(a) recordkeeping	5,713	1	5,713	40	228,520
312.62(b) recordkeeping	5,713	12.5	71,355	40	2,854,200
312.160(a) recordkeeping	1,432	7.5	10,708	0.5	5,354
312.160(c) recordkeeping	1,432	2.5	3,573	0.5	1,786.5
Total biologics recordkeeping hours					3,376,325.5
Total biologics burden hours					3,337,740.5
Subtotal					6,714,066
Human Drugs					29,326,763
Biologics					6,714,066
Total					36,040,829

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: 10-11-02

October 11, 2002.

Margaret M. Dotzel,
Associate Commissioner for Policy.

[FR Doc. 02–????? Filed ??–??–02; 8:45 am]

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